REMARKS/ARGUMENTS

Claims 83, 84, 86, and 106-134 are pending. Claims 82, 85, 87-105 are cancelled, claims 83, 84, and 86 are amended, and claims 106-134 are added. No new matter has been added.

Applicant has amended the claims to recite a pharmaceutical composition having a microstructure not taught by the prior art. Applicant recites a pharmaceutical composition composed of gabapentin crystals having a *mineral acid dispersed throughout each gabapentin crystal* in small amounts. The mineral acid is present in an amount sufficient to provide to the crystals at least 20 ppm of the anion of the mineral acid, based on the weight of gabapentin. Anions of mineral acids include, for example, chloride & bromide ions. The recited pharmaceutical compositions are distinguished from conventional gabapentin hydrochloride crystals which has a chloride ion content significantly higher than the presently recited compositions, i.e., at least 10,000 times greater.

Applicant thanks the Examiner for holding the teleconference of July 15, 2004 to discuss the Singer patent and the Applicant's new claims. During the teleconference, Applicant's proposed newly recited gabapentin crystal microstructure was favorably received in view of the compositions and methods described by the Singer patent. The product-by process claims proposed by the Applicant were also favorably received in view of the Singer patent assuming that the Applicant could show a difference between the resulting compositions. Applicant noted that the compositions could be distinguished based on stability data. The Applicant has identified the pertinent stability data below. None of the new claims enclosed herein were pending as of the time of the teleconference so no agreement of patentability was reached.

Claims Rejections - 35 U.S.C. 112,2d para.

In the Office Action, claims 82-91, 94, and 95 have been rejected 35 U.S.C. 112, 2d para. as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention because the term "susceptible" is vague. This rejection is respectfully traversed.

Applicant respectfully disagrees that the term "susceptible" is vague because one skilled in the art would have no difficulty identifying conditions that cause amino acids to degrade. As is well known by those skilled in the art, some cyclic amino acids degrade by a dehydration reaction that leads to cyclization to a lactam compound. Compounds that degrade via this process are described in, for example, the Augart patent, and U.S. Patent Nos. 4,087,544 & 5,084,479. This degradation reaction is described in, for example, U.S. Patent No. 6,054,482 to Augart (the Augart patent).

Therefore, the art skilled would know what conditions would cause an amino acid to degrade. Accordingly, Applicant respectfully requests withdrawal of this objection under 35 U.S.C. §112, second paragraph.

Claims Rejections - 35 U.S.C. §102(b) & §102(e)

In the Office Action, claims 82-91, 94-95 have been rejected under 35 U.S.C. §102(b) as allegedly being unpatentable over WO 98/28255. Claims 95-105 have been rejected under 35 U.S.C. §102(b) as allegedly being unpatentable over the Singer patent. This rejection is respectfully traversed because the cited art does not teach each element of the pending claims.

In contrast to the claimed composition, the Singer patent describes gabapentin formulations that *do not have a mineral acid dispersed throughout gabapentin crystals* in small amounts. Although the Singer patent describes gabapentin formulations having at least 20 ppm of an anion of a mineral acid, anions of a mineral acid present in the formulations are necessarily found outside of the gabapentin crystal structure, i.e, bound to a strong base such as for example an amine. As described below, the difference in the distribution of anions of a mineral acid provides a different formulation microstructure that yields substantial differences in stability.

The Singer patent describes methods of preparing pharmaceutical compositions by first washing gabapentin hydrochloride with alcohol to remove impurities. See, e.g., Example 1. Then, gabapentin hydrochloride is dissolved in ethylacetate. See Col. 4, lines 3-27. A strong base, e.g., tributylamine, a substance with a high affinity for anions, is added to react with, and bind to, chloride anions that are in the ethylacetate solution to form tributylamine chloride. The gabapentin precipitates out of solution and the tributylamine chloride is removed by filtration. Upon drying the filtered product will include raw gabapentin crystals and residual tributylamine chloride. The chloride ion content of the filtered product is about 4-40 ppm. See Table 1. The dried gabapentin crystals in this raw material admixture are necessarily free of chloride anions because the chloride ions have been bound to tributylamine while in solution. The chloride ions remain separate from the gabapentin crystals after drying in the residual tributylamine chloride. Indeed, removing chloride ions from the gabapentin is the very purpose for adding tributylamine.

The raw material admixture of gabapentin crystals and tributylamine chloride is then dry-mixed with adjuvants, such as for example, corn starch and cellulose. See, e.g., Example

17-19, col.11, lines 24 & 25. Next, the admixture is suspended/dissolved in water for aqueous granulation. While in solution any free chloride anions are again drawn to, and bound by, tributylamine to form tributylamine chloride. Upon drying, the tributylamine chloride forms crystals that are dispersed throughout the entire composition, not within the gabapentin crystals.

Nowhere does the Singer patent describe pharmaceutical formulations having a microstructure wherein a mineral acid, for example HCl, is dispersed throughout gabapentin crystals in small amounts as recited in the pending claims. Indeed the Singer patent describes methods for removing all anions of a mineral acid from gabapentin crystals.

The difference between the composition microstructure of the Singer patent and the recited claims is readily illustrated by comparing stability properties. A comparison of the stability of both compositions shows that the presently recited compositions are more stable, i.e., experience less degradation over the same shelf life, despite having greater than 20 ppm of an anion of a mineral acid.

For comparison of stability, Applicant's Example 7 was prepared using methods similar to the Singer patent. Example 7 utilized gabapentin raw material having 15 ppm of an anion of a mineral acid which is similar to the starting material obtained in Example 1 of the Singer patent, i.e., Run F. In Example 7 the gabapentin raw material was combined with various adjuvants and *granulated with water* which is similar to the techniques for preparing dosage forms as described in Example 17-19 of the Singer patent. As shown in Applicant's Table 6, the dosage forms prepared according to Example 7 exhibited **1.13 weight percent**

lactam after 90 days at accelerated storage conditions.[1] In contrast, Applicant's Example 2 utilized the gabapentin raw material having 15 ppm of an anion of a mineral acid of Example 7, except that it was *treated (wetted) with an alcoholic HCl solution* before being admixed with adjuvants. The alcoholic HCl solution is a stabilizing solution that dispersed mineral acid throughout the gabapentin crystals in small amounts as in the recited claims. This formulation was not granulated with a liquid but simply dry mixed. As shown in Applicant's Table 6, the dosage forms prepared according to Example 2 exhibited only **0.05 weight percent lactam**, i.e., less than the compositions similarly described in the Singer patent.

Similarly, Applicant's Example 5 utilized the gabapentin raw material having 15 ppm of an anion of a mineral acid as Example 7 & 2, except that it was *treated (wetted) with an alcoholic HCl solution* before being admixed with adjuvants *and granulated with alcohol*. As shown in Applicant's Table 6, the dosage forms prepared according to Example 5 exhibited only **0.49 weight percent lactam**, i.e., less than the compositions similarly described in the Singer patent.

Although the Singer patent describes compositions that are purportedly stable with greater then 20 ppm of an anion of a mineral acid, it is well known that gabapentin compositions are less stable as the concentration of anion of a mineral acid increase. See, e.g., U.S. Patent No. 6,054,482 to Augart. Thus, Applicant's Example 7 having 15 ppm of an anion of a mineral acid would be more stable, i.e., less lactam would form, compared to

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1 The recited stability conditions of 3 months at 40 degrees Centigrade and 75 % relative humidity is the FDA approved testing condition for accelerated measurement of stability. Accelerated stability data is utilized to grant drug expiration dates of up to **2 years**. Therefore, Applicant's stability conditions measure long term stability whereas the stability conditions described in the Singer patent represent short term stability up to **1 year**. Gabapentin degrades at a non-linear rate thereby preventing a side by side comparison of stability data.

compositions having more than 20 ppm of an anion of a mineral acid when stored at the same conditions.

As with the Singer patent, WO 98/28255 does not teach the recited pharmaceutical compositions composed of gabapentin crystals having a *mineral acid dispersed throughout the crystal structure* in small amounts. Accordingly, since the Singer & Vilkov patents and WO98/28255 do not teach all of the elements of Applicant's claims, withdrawal of the rejections under 35 U.S.C. §102(b) & §102(e) is requested.

Claims Rejections - 35 U.S.C. §103(a)

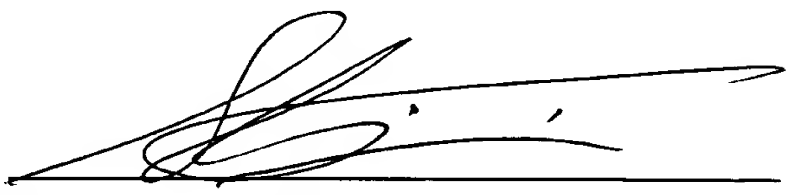
In the Office Action, claims 82-91 and 94-105 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,294,198 to Vilkov (the Vilkov patent). This rejection is respectfully traversed because the cited art does not teach or suggest the invention recited in the newly added claims.

There is no suggestion for one of ordinary skill in the art to modify the Vilkov patent to achieve stable gabapentin dosage forms composed of gabapentin crystals having a mineral acid dispersed throughout each crystal in small amounts as recited in the pending claims. Further, Vilkov does not suggest stabilizing gabapentin crystals with an alcoholic hydrochloride solution. Without such a suggestion, the present claims cannot be found obvious over the Vilkov patent. Therefore, the cited references do not teach or suggest all the limitations of the pending claims. Accordingly, withdrawal of the rejection under 35 U.S.C. §103(a) is requested.

CONCLUSION

Applicant believes that the foregoing is a full and complete response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and allowance of all of pending claims 83, 84, 86, and 106-134 are respectfully requested.

Date: July 15, 2004



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